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DOCTORAL THESIS SUMMARY

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PARTICULARITIES OF RENAL DISEASES IN PREGNANCY

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Key words: pregnancy, renal disease, urinary tract infection, ureterohydronephrosis, chronic kidney disease, acute kidney injury, preeclampsia, gestational arterial hypertension, foetal complications, maternal complications

INTRODUCTION

Before 1980, there were different opinions about influence of kidney disease on pregnancy or its impact on maternal kidney disease, as well. The initial studies were anecdotal, covering limited patients' group, with reports before updated current therapies. Recent advances in medicine have made it possible to better understand different pathologies, to establish adequate early diagnosis and improve therapeutical management during pregnancy. Physiological changes in pregnant women have an important impact upon kidney structure and functions, creating sometimes difficulties in interpretation of biological tests and establish the correct diagnosis. In spite of all these conditions, most of these pregnant women can carry on the pregnancy in optimal conditions, only few of them needing earlier or urgent caesarean section for maternal and foetal safety.

This study is an in-depth approach of entire renal pathology associated to pregnancy, with the aim of monitoring kidney disease as pregnancy progresses and trying to establish the correct therapeutical steps of management of this pathology.

Our work is structured into 2 studies:

1. **Epidemiological and clinical features of renal pathology during pregnancy**
2. **Utility of sFtl-1/PIGF ratio and serum albumin in the assessment of placental hypoxia in preeclampsia**

Study no. 1: Epidemiological features of renal pathology during pregnancy

In this study we have collected data necessary for clinical and epidemiological of renal pathology associated to pregnancy in Constanta County Emergency Clinical Hospital. Given that the information in the literature is relatively scarce, at national and international level as

well, such as analysis is necessary, the aim of the study isn't to achieve a clinical and epidemiological profile of renal diseases that may develop with pregnancy.

The first study was divided into 4 parts, designed to create an image about kidney disease in pregnant women in Constanta:

a. General characteristics of pregnant women with renal pathology

b. Characteristic of urinary tract infections in pregnancy

c. Early diagnosis and management of ureterohydronepohrosis during pregnancy

d. Characteristics of chronic kidney disease in pregnancy

The aim of the research presented in subchapter *„General characteristic of pregnant women with renal pathology*" was to establish an epidemiological profile of pregnant women in Constanta county, according to maternal age, gestational age, origin, parity; the research also included analysis of potential association between parity and gestational age. We considered that this information would be useful for our region, as there are few epidemiological data published in the national literature regarding this subject. The aim was to establish the frequency of each type of renal disease associated to pregnancy, with the purpose of analysing them in subsequent chapters. Pregnant women with renal disease were the central point of this study, being designated in the first line: urinary tract infections, pathological ureterohydronephrosis, chronic kidney disease at different stages and variable causes, acute kidney injury and preeclampsia.

The aim of subchapter *„Characteristic of urinary tract infections in pregnancy"* was to make an epidemiological profile of UTI, regarding their clinical manifestations, risk factors and specific etiology, on a group of patients hospitalized in Constanta County Emergency Clinical Hospital in a well-established interval of time. Association of clinical forms with the trimester of pregnancy and maternal hydronephrosis was realized in order to guide physicians in their decision of management and possibly prediction of a successful pregnancy.

Subchapter „*Early diagnosis and management of ureterohydronephrosis during pregnancy"* started with analysing the development of physiological ureterohydronephrosis during pregnancy, followed by the frequencies regarding gestational age, locations and grade of impairment. Associations were made between right/left ureterohydronephrosis grade with gestational age and parity of pregnant women. Analysing the grades of ureterohydronephrosis at different gestational ages our aim was to assess its impact on pregnant women representing an essential and definitory step in taking decisions regarding the therapeutical approach.

Subchapter *„Characteristics of chronic kidney disease in pregnancy"* assesses the description of different chronic kidney disease associated to pregnancy, analysing their influences on this condition. The influence of pregnancy on the progression of chronic kidney disease and therapeutical approach in case of exacerbation or onset were not omitted. Other important issues discussed were maternal or foetal complications in the evolution of pregnancy, the results being of great interest to the physician who must take a correct decision of therapeutical management in order to obtain a successful pregnancy and reduce maternal and foetal risks.

Acute renal injury had a low frequency in the study group and was superimposed with the pathologies listed above, which is why it was described in the chapter corresponding to associated renal pathology, thus not requiring a separate approach.

In the second study of this thesis we analysed pregnant women with preeclampsia, this special condition requiring a separate clinical, biological and therapeutic approach.

Study no. 2: Utility of sFtl-1/PIGF ratio and serum albumin in the assessment of placental hypoxia in preeclampsia

This study is to evaluate preeclampsia in term to establish a correct diagnosis and the role of sFtl-1/PIGF, as well as the involvement of serum albumin in severity of preeclampsia and its association with maternal and foetal complications. The purpose and practical contribution of the final results is to help the multidisciplinary team in taking adequate therapeutical decisions, as literature data has been poor in information about this pathology, at least at the national level being completely absent until now.

Study number 2 focused on the following ideas:

a. *General findings of clinical and paraclinical characteristics of the studied groups (preeclampsia, gestational hypertension, control group)*
b. *Utility of sFtl-1/PIGF ratio in diagnosis of preeclampsia*
c. *Severity of preeclampsia and potential association with serum albumin*

By documenting the clinical and paraclinical characteristics of studied groups, we follow to create a general image of preeclampsia. For each group, the points analysed were clinical features (maternal age, parity, origin, gestational age at onset, gestational age at birth, birthweight) and paraclinical features (proteinuria/24 hrs, serum creatinine, uric acid, liver enzymes, platelets, serum albumin). Starting from the idea that in the middle of preeclampsia

aetiology is placental ischemia and disorder of angiogenic markers (sFtl-1, PIGF), the literature data suggests that abnormal sFtl-1/PIGF ratio is associated with preeclampsia. The specific value of sFtl-1/PIGF ratio was established for each studied group and was analysed according to gestational age at onset and severity of preeclampsia. The aim of the study was to establish a practical utility of sFtl-1/PIGF ratio in diagnosis and severity of preeclampsia. Another important aspect pointed in this study was association of high values of sFtl-1/PIGF ratio with remaining duration till end of pregnancy providing a prediction of pregnancy associated with preeclampsia.

The association of serum album with preeclampsia severity was analysed with the aim of introducing a value less than 3 g/dL as marker of severity. We also approach foetal and maternal complications that can occur during pregnancy with gestational or normotensive hypertension, demonstrating the need to establish an adequate management in order to reduce maternal and foetal risks, and to achieve a successful pregnancy.

CURRENT STATE-OF-THE-ART

The first chapter **„Renal morpho-functional changes during pregnancy"** describes the adaptative processes necessary for foetal growth. Due to water retention in pregnancy, glomerular filtration will increase, leading to nephromegaly. Simultaneously with increased renal size, hydronephrosis is the most common renal anatomical change in pregnancy, but sometimes could represent a pathological condition [8]. Increased glomerular filtration rate and adjustment of tubular renal function causes an increased tubular excretion of creatinine, blood urea nitrogen and uric acid, that will lead to the decreasing of their serum levels. Approaching in details of these anatomical and functional changes described in the literature data, our study aimed to define a protocol of early detection of renal changes, that could lead to adequate therapeutical decisions, in order to have a successful pregnancy, both for the mother and the foetus, but also for the medical team involved.

The second chapter **„ Urinary tract infections in pregnancy**" describes data from literature about particularities of infectious renal pathology that can develop during pregnancy. About 80% of pregnant women have urinary stasis, leading to deterioration of physiological anti-reflux mechanism, favouring bacterial growth and upward spread of infection. Biochemical urinary changes specific to pregnancy can also be added at these predisposing factors [56]. Urinary tract infections in pregnant women are classified into 2 different categories***: asymptomatic bacteriuria*** and ***symptomatic infections.*** Urinary tract infections are

considered complicated infection during pregnancy, with particularities in approaching to clinical diagnosis and appropriate therapy, in order to reduce the risk of progression to acute pyelonephritis and sometimes preeclampsia, and foetal consequences, like premature birth and intrauterine growth restriction [62].

The third chapter **„Hypertension and pregnancy"** describes the etiopathogenesis and pathophysiological impact of pregnancy in developing arterial hypertension. High blood pressure is the most common pathology developed in pregnancy, complicating 10% of pregnancies. Hypertension in pregnancy can be divided into 4 categories [106]: ***chronic hypertension, preeclampsia-eclampsia, superimposed preeclampsia on chronic hypertension*** *and* ***gestational hypertension.*** Subchapter ***„Etiopathogenesis of preeclampsia"*** presents the various hypothesis existing in the literature data about the development of this pathology, this topic representing still an interest for recent studies. The pathophysiological steps involved would be placental ischemia and release of angiogenic factors. Recent studies suggest that in the middle of preeclampsia aetiology is imbalance between ***pro-angiongenic factors*** (PIGF, VEGF) and ***antiagiogenic factors*** (sFtl-1/sEng) [132]. The other subchapters describe the key diagnostic elements of gestational hypertension and preeclampsia, including complications like Eclampsia, HELLP syndrome. Other data analysed are the therapeutic strategy for each pathology needed to achieve a successful pregnancy, data being taken from the literature and improved with current studies.

The chapter „**Acute kidney injury and pregnancy**" describes the main causes of acute injury specific to pregnancy. In addition to those covered in the previous chapters (preeclampsia, sepsis), there are some particular forms of AKI specific to pregnancy which are described: acute tubular necrosis and acute cortical necrosis. Another detailed aspect was to establish the adequate definition of acute kidney injury in pregnant women, being well known that increasing glomerular filtration rate during pregnancy will decrease serum creatinine. Most authors define acute kidney injury in pregnancy by increasing serum creatinine above 1 mg/d L and/or increasing by ≥ 0,3-0,5 mg/dL compared to the previous creatinine level, in less than 48 hours. In recent decades, the incidence of acute kidney injury has decreased due to improved prenatal care, rapid detection of pathological conditions and optimal initiation of therapy. In developed countries, the rate of acute kidney injury in pregnant women is declining [191].

The chapter **„Chronic kidney disease and pregnancy"** describes the effects of pregnancy on renal function and progression of CKD, as well the aspects necessary to monitor pregnant woman with this kind of pathology. Pregnancy monitoring should include frequent antenatal visits to assess blood pressure, weight gain, kidney function, albuminuria and detect

possible urinary tract infections. Renal function should be followed monthly by monitoring serum creatinine, urea, serum electrolytes and estimated glomerular filtration rate [206]. The subchapter „Evolution features according to primary renal disease" describes the particularities of glomerular, tubular and interstitial nephropathy that develop chronic kidney disease, data being collected from specific studies.

Concerns about risks of maternal mortality in the context of severe, acute or chronic renal failure have decreased in recent years, it being well known that a pregnancy which is associated with a severe renal impairment can be controlled by initiating renal replacement therapy.

STUDY 1: Epidemiological features of renal pathology during pregnancy

Objectives:

The main objective of the present study was to achieve an epidemiological profile, characteristic for pregnant women with renal pathology, monitored in the Constanta County Emergency Clinical Hospital, with the following secondary objectives:

- Establishing the total number of pregnancies that associate renal pathology hospitalized in Constanta Emergency Clinical County Hospital,
- Assessment of heterogeneous groups characterized by renal pathology superimposed on pregnancy with effects on the structure or function of renal function and determination of the impact and evolution of kidney disease on the maternal organism
- Evaluation of urinary tract infections (UTIs) and associated risk factors among pregnant women
- Carrying out a cartographic projection on the etiopathogenesis of urinary tract infections that occurred during pregnancy with the purpose to prevent or modify their severity and evaluating the therapeutic strategies used to reduce maternal and fetal risk.
- Evaluation of the anatomical changes given by the pregnancy and the association with the gestational age of the pregnant woman
- Monitoring of the symptoms given by ureterohydronephrosis (UHN) and the optimal therapy in these cases
- Monitoring the evolution of chronic renal disease (CKD), in different stages and of variable causes, associated with pregnancy and maternal or fetal complications in its evolution

- Distribution of renal pathology according to the patient's age, pregnancy age, trimester of pregnancy, environment of origin, parity, complications, followed treatments and physiological changes associated with this condition.

Material and methods:

The present study used a prospective and descriptive plan, aiming to analyse simultaneously several predominant features of renal pathology during pregnancy (either diagnosed before pregnancy or occuring during pregnancy, usually on a previously healthy kidney). Data were collected from blood and urine samples, as well as data obtained by ultrasonography, performed on 247 patients who were hospitalized between 01.05.2017-01.05.2021 in the Nephrology Clinic and Obstetrics-Gynecology Clinics of the Emergency Clinical County Hospital of Constanta. Some patients needed reassessments during the same hospitalization, due to their evolution burdened with complications. All information was carefully retrieved and recorded in the database, which included demographic (pregnancy age, patient age, personal pathological history), and clinical-biological and imaging data (ultrasonography), diagnosis, therapeutical measures, and maternal and fetal complications. The results of the study were analyzed with IBM SPSS Statistics 23 software. The procedures used were descriptive statistics, graphs and nonparametric statistical tests to confirm various hypotheses that were subsequently verified with recent data from the literature.

Results

Renal pathology encountered in the study group was distributed as follow : acute renal pathology- 224 pregnant women (90.69%) and chronic renal pathology- 23 pregnant women (9.31%).

UTIs were present in 175 pregnant women (70.85%) of the total group, **UHN** in 138 pregnant women (55.87%), **CKD** in 23 pregnant women (9.31%) and **Preeclampsia** in 59 pregnant women (23.9%). **AKI** in the study group was present in 25 pregnant women (10.12%), of which :

- 23 patients had an AKI caused by complications of urinary tract infections, ureterohydronephrosis and exacerbation of previous kidney disease, the cases being detailed in that pathology description.
- 1 pregnant woman with renal AKI due to nephrotoxicity to NSAIDs
- 1 pregnant woman with prerenal AKI due to a hemorrhagic shock at birth resulting in maternal and fetal death.

Characteristics of urinary tract infections in pregnancy

Of the total of 247 patients included in this study, 175 (70.85%) had at least one episode of UTI with different clinical forms. Their distribution by trimester of pregnancy was as follows: 72 pregnant women in the first trimester (41.14%), 35 pregnant women in the second trimester (20.0%) and 68 pregnant women in the third trimester (38.86%). 123 (70.29%) of pregnant women had favorable conditions and detectable risk factors such as ureterohydronephrosis, kidney stones, polycystic kidney disease, simple kidney cysts, chronic pyelonephritis and diabetes, The clinical manifestations of UTI in our study group were distributed as follows : 36 (20.57%) asymptomatic bacteriuria, 56 (32.0%) acute cystitis, 44 (25.14%) recurrent lower urinary tract infections, and 39 (22.29%) acute pyelonephritis.

Pregnant women with acute pyelonephritis had the highest frequency in the third trimester of pregnancy (71.8%, 28/39), followed by those in the first and second trimesters (12.8%, 5/39; respectively 15.4%, 6/39). Analysing a possible association between the development of acute pyelonephritis and the trimester of pregnancy, it was shown that the proportion of those in the third trimester is the highest (41.2%, 28/68), being significantly different ($p = 0.01 < 0.05$) from those in second trimester (14.3%, 5/35). The proportion of pregnant women with acutepyelonephritis in the first two trimesters were not significantly different (8.3%, 6/72, respectively 14.3 5/35; $p = 0.535 > 0.05$. Analyzing the association of acute cystitis with the trimester of pregnancy, the proportion of pregnant women in the first and second trimester were significantly different ($p < 0.001$), the group in the first quarter having a higher proportion than in the second trimester (59.7%, 43/72; respectively 20.0%, 7 / 35), on the other hand, the proportion of acute cystitis in the last two trimester were low, the two groups not being statistically significantly different (20.0%, 7/35, respectively 8.8%, 6/68, $p > 0.05$).

Regarding the etiology, the germs involved in the study group UTIs had the following distribution: Escherichia Coli -73 (41.71%), Klebsiella pneumoniae -32 (18.29%), Enterococcus faecalis -22 (12.57%), Proteus mirabilis -12 (6.86%), Staphylococcus aureus -6 (3.43%) and unidentified germs (sterile urine culture) but symptomatic UTIs- 30 (17.14%). The therapy adopted in the study group included antibiotic, adjuvant and symptomatic therapy selected from a range of safe drugs during pregnancy. Antibiotic therapy used included : Ampicilline (60 patients - 34.29%), Amoxicilline + Clavulanic Acid (18 cases -10.29%), Cephalosporins (74 cases-42.29%), Quinolones (11 cases-6.29 %) and Nitrofurantoin (12 cases-6.86%). Out of the 175 pregnant women with UTI, there were 10 patients (5.71%) who

had an unfavorable evolution, needing the association of Carbapenems (Meropenem). The recurrence rate of UTIs was 22.28% (39 of 175 pregnant women).

Maternal complications were represented by AKI for 7 cases, one of which ended with death of the pregant woman due to septic shock and 3 cases with exacerbation of chronic kidney disease, the basic renal pathology being chronic pyelonephritis (1 case with CKD progressing irreversibly from stage G2 to G3b) and diabetes mellitus. All of the 3 cases developed sepsis, 2 of which ended in death. The rest of the pregnant women with AKI had ureteral lithiasis (3 cases), the clinical form involved being acute pyelonephritis. *Foetal complications* accounted for 6.85% (12 cases) of the total number of cases included in the study. Regarding the association between complications and the clinical form of UTI, from the 39 pregnant women with acute pyelonephritis, prematurity was present at 20.5% (8/39 cases) and intrauterine growth restriction at 10.2% (4/39 cases). *Mortality* in the study group with UTIs was 1.71% (3 cases) by toxic-septic shock and disseminated intratravascular coagulation.

Early diagnosis and management of ureterohydronepohrosis during pregnancy

The UHN frequency in the group of 247 pregnant women included in the present study was 138 (55.87%) patients. Depending on the trimester of pregnancy, the pregnant women in the study group were distributed as follows : 35 (25.36%) in the second trimester and 103 (74.64%) in the third trimester.

Depending on the location of UHN, the study group was divided as follows : right UHN -138 pregnant women (100%), respectively left UHN- 94 pregnant women (68.12%). Depending on the right UHN grade, the group included 50 pregnant women (36.23%) with right UHN grade II and 88 pregnant women with right UHN grade III (63.77%). Right UHN grade IV was not present in the patients included in our study. Depending on the left UHN grade, the studied group included 30.43% (42/138 pregnant women) with left UHN grade I and 37.68% (52/138 pregnant women) with left UHN grade II. Grade III and IV of left UHN was not present in the patients included in the study. The gestational age of UHN patients included in the study ranged from a minimum of 23 weeks to a maximum of 38 weeks, with a mean value of 30.98 and a standard deviation of 4.14.

The results showed that **there is a an association between gestational age and right UHN grade:** $\chi 2calc = 21.18$, $df = 3$, $p < 0.001 < \alpha = 0.05$.

Table X. Association between grade of right UHN and Gestational age (weeks)

Grade of right UHN	Gestational Age(weeks)				Total
	22-26	27-31	32-36	37-41	
Grade II (no. pregnant women)	18	14	13	5	50
% gestational age (weeks)	78.3%	26,4%	28.9%	29,4%	36.2%
Grade III (No. pregnant women)	**5**	39	32	12	88
% gestational age (weeks)	21,7%	73,6%	71,1%	70,6%	63.8%
Total	**23**	**53**	**45**	**17**	**138**

Also, it was described **an association between gestational age and left UHN grade**: $\chi^2_{calc} = 12,17$, df = 2, p = 0.02 < α = 0.05.

Table XI. Association between grade of left UHN an d Gestational age(weeks

Grade of left UHN	Gestational Age (weeks)			Total
	27-31	32-36	37-41	
Grade I (No. of pregnant women)	26	11	5	42
% gestational age (weeks)	65.0%	26.8%	38.5%	44.7%
Grade II (No. Of pregnant women)	14	30	8	52
% gestational age (weeks)	35.0%	73.2%	61.5%	55.3%
Total	**40**	**41**	**13**	**94**

Analysing data from our study, regarding the association between UHN grades' and gestational age, it was observed that the highest grade of UHN had the most important proportion after 27 weeks of pregnancy for right UHN, respectively after 32 weeks of pregnancy for left UHN, these remarks being significantly different from UHN of the following weeks ($p < 0.001$);

Out of a total of 138 pregnant women with UHN, 73.19% (101 patients) had ipsilateral lumbar pain associated with ureterohydronephrosis, as a marker of a pathological UHN. The intensity of low back pain was estimated according to the VAS scale, so the frequency of mild back pain was 16.67% (23 pregnant women), respectively moderate intensity of 36.23% (50 pregnant women) and severe intensity of 20.29%. UHN was complicated by UTI in 92 pregnant women (66.67%), the clinical forms involved being represented by: asymptomatic bacteriuria

(15.22% -14 cases), acute cystitis (14.13% -13 pregnant women), recurrent lower UTIs (40, 22% - 37 pregnant women) and acute pyelonephritis (30.43% - 28 pregnant women).

Out of a total of 138 pregnant women, 16 patients (11.59%) had ass a ureteral stone (figure 31) and the AKI started at 7.97% of the study group (11 pregnant women / 138). The treatment included analgesics (No-Spa, Algocalmin, Paracetamol), antibiotics (Cephalosporin / Ampicilline / Nitrofurantoin / Chinolone / Amoxicilline), adjuvant therapy (herbal products containing cranberry ± methylene blue) and adequate hydration. Symptoms improved in 88.40% of cases (122/138 pregnant women). Of the 16 cases complicated by ureteral lithiasis, 11 pregnant women developed AKI recovered their kidney function after inserting ureteral stents by urological surgery, 3 pregnant women after NSAIDs withdrawal and administration of low doses of corticosteroids and the last 2 required emergency cesarean delivery. The inserted stents did not involve any complications and were removed after delivery.

Characteristics of chronic kidney disease in pregnancy

The frequency of chronic kidney disease (CKD) was 9.31% (23 pregnant women) of the total of 247 patients. Depending on the underlying renal pathology and the stage of renal disease on entering our study, the pregnant women could be distributed as follows:

- 9 pregnant women with glomerular nephropathy:
  - o 3 cases with lupus nephropathy (2- CKD stage G3b, 1- CKD stage G4)
  - o 1 case of membranous GN (CKD stage G1)
  - o 2 cases with minimal change disease/glomerulopathy (CKD stage GI)
  - o 1 case with Ig A nephropathy (CKD stage G3a)
  - o 1 case with diabetic nephropathy (CKD stage G5-predialysis)
  - o 1 case with Alport syndrome (CKD stage G1)
- 4 pregnant women with chronic pyelonephritis (3-CKD stage G2, 1-CKD stage G3b)
- 8 pregnant women with polycystic kidney disease (6 -CKD stage G1, 2- CKD stage G2)
- 2 pregnant women in HD program at the entrance to the study
- 1 pregnant woman with diabetic nephropathy (CKD stage G5-predialysis)

Table XII. Evolution of glomerular nephropathy

Glomerular nephropathy	**Onset**	**Exacerbation/ Nephrotic syndrome**	**Treatment+Evolution**
Lupus nephropathy (3 patient)	3rd Trimester	1 patient with proteinuria5,6g/24h -2 patients- Stable CKD	high dose of cortizon => reducing level of proteinuria
IgA Nephropathy	Stable CKD during all evolution of pregnancy , without exacerbation or complication		
Alport Syndrome	3rd Trimester	Proteinuria 13g/24h +hypoalbuminemia +high BP	***Caesarean delivery*** +Methylprednisone ,followed by oral Pednison Remaining proteinuria at 3 months (0,5-1,2 g/24 h) Biopsy: Alport syndrome
Membranous Nephropathy	2ndTrimester	Proteinuria 5,3g/24h + hypoalbuminemia	Prednison =>increased proteinuria in 3rd Trimester (7 g/24 h)+high uric acid+high BP+ seizures in the first 24 h of onset (Eclampsia) **=> *Cesarean delivery*** + Methylprednisone, followed by oral Pednison Remaining proteinuria at 3 months (0,5-1,2 g/24) with Biopsy- membranous nephropathy
Minimal change glomerulopathy (2 patients)	3rd Trimester	Proteinuria 3,9g/24h,respectively proteinuria 5,7g/24h	Oral Cortisteroid with remission of protenuria No need for kidney biopsy

Given the evolution of renal disease during pregnancy, the patients with CKD included in the study could be divided into 2 categories as follows: 15 pregnant women with CKD without changes of renal function during pregnancy and 8 pregnant women with CKD whose evolution included aggravation of underlying kidney disease The exacerbations in the studied group were due aggravating proteinuria in nephrotic syndrome in 5 cases; the underlying disease was lupus nephritis, membranous nephropathy, Alport syndrome and 2 minimal change glomerulopathy, and in 3 cases urinary tract infections, complicated with septic shock and intravascular disseminated coagulation due to acute-on-chronic pyelonephritis and brittle diabetes.

Table XIII. Complications of CKD during pregnancy

Underlying CKD	Maternal complications	Fetal complications
Chronic pyelonephritis (4 women)	urosepsis + disseminated intravascular coagulation progression of kidney disease *(stage 2-> stage 3b)*	Prematurity Intrauterine growth restriction
	urosepsis- septic shock ***(death)***	Intrauterine growth restriction
	2 cases with lower UTIs	
Polycystic renal disease (6 women)	lower UTIs	None
Diabetic nephropathy	urosepsis + disseminated intravascular coagulation ***(death)***	Intrauterine death
Lupus nephropathy (2 women)	progression of kidney disease *(stage3b-> stage 4)*	
	lower UTIs	
Minimal change GN (2 women)	Preeclampsia	
	Preeclampsia	Prematurity
Membranous glomerulopathy	Preeclampsia + Eclampsia	
Hemodialysis (2 women)		Spontaneous abortion
		Hydrocephalus Prematurity

Main conclusion: Treatment of previous renal disease during pregnancy is a real challenge for nephrologists, considering approaching adequate therapy and exposure to maternal or foetal risks related not only to the disease itself, but to drug therapy, as well. The patients with underlying kidney disease, attributed to different etiologies, should be strictly monitorized during pregnancy, for both maternal and foetal safety.

General conclusions:

1. Renal pathology has a high frequency during pregnancy,
2. Regarding renal pathology, UTIs have the highest frequency during pregnancy.
3. CKD and AKI are rarefindings during pregnancy.
4. UHN is a relatively common anatomical change during pregnancy.
5. All clinical forms of UTIs could be present during pregnancy, but the most common are lower urinary tract infections, the most involved germs being E. Coli.
6. UHN is a factor that influences the occurence of UTIs, being the most common favourising condition.

7. UHN is associated with the gestational age, the degree of UHN increasing proportionally with it. Primiparity is also associated with an increased risk of developping UHN.

8. In the majority of the cases, pathological UHN could be solved with conservative treatment.

9. Pregnancy may accelerate the progression of CKD in selected cases, and may impose the initiation of renal replacement therapy (haemodialysis).

10. The nephrotic syndrome diagnosed in the last trimester of pregnancy as preeclampsia has a favorable evolution after the end of pregnancy/delivery.

11. The foetal risks associated with renal pathology are represented by prematurity and low birth weight.

12. A multidisciplinary team of nephrologists and gynecologists is needed to successfully pregnancy, with the need of pregnant women counseling before and during pregnancy.

STUDY 2: Utility of sFtl-1/PIGF ratio and serum albumin in the ~~assement~~ assessment of placental hypoxia in preeclampsia

Objectives

The main objective of this study was to perform a clinical and biological profile of pregnant women with preeclampsia in Constanta County Emergency Clinical Hospital and to evaluate the use of sFtl-1/PIGF in diagnosis of PE, with the following secondary objectives:

- Establish the total number of pregnancies associated with preeclampsia (PE) in patients monitored in the Constanta County Emergency Clinical County Hospital;
- Determine a biological profile of PE and gestational hypertension (GH) and its association with serum albumin levels;
- Establish the values of sFtl-1/PIGF specific to PE, GH and non-PE pregnant women (control group);
- Determinate the association between sFtl-1/PIGF ratio with severity of PE, GH and non-PE pregnant women (control group);
- Evaluation of sFtl-1/PIGF ratio depending on PE severity and its onset;
- Establish the association between sFtl-1/PIGF ratio with remaining duration until the end of pregnancy;
- Evaluation of maternal and foetal complications appeared in PE and association with the serum albumin values.

Material and methods

Our study used a prospective and descriptive plan based on a group of pregnant women with PE (59 pregnant women) which was compared with 2 non-PE groups (GH - 25 pregnant women and the control group - 43 pregnant women) between 01.05 2017- 01.05. 2021, who addressed to Constanta County Emergency Clinical Hospital for hospitalisation on the Gynaecology and Nephrology Department, with follow-up visits. The clinical variables followed were: maternal age, origins, parity, gestational age at onset, severity, duration till ending of pregnancy from sFtl-1/PIGF testing, gestational age at birth, foetal birth weight and blood pressure values , maternal and foetal complications. In order to complete the biological profile, the following variables were determined: proteinuria / 24h, serum albumin, PE markers (sFtl1, PIGF, sFtl-1 / IPGF ratio), uric acid, serum creatinine, complete blood count (especially platelet count) and liver enzymes ALT, AST). Experimental data were processed using IBM SPSS Statistics 23 and MedCalc 14.8.1. The procedures used were: Descriptive statistics, Graphs, Parametric statistical tests, Non-parametric statistical tests for categorical variables, Non-parametric statistical tests for ordinal data or for numerical variables when the normal condition was not satisfied, ROC curves analysis.

Results

Clinical and paraclinical features of the studied groups (PE, GH, Control group)

The study included 59 (46.46%) pregnant women with PE, 25 (19.69%) pregnant women with GH and 43 (33.86%) pregnant women with non-PE (control group).

Table XVII. Clinical findings of studied groups

		PE	**GH**	**Control**	***p***
No. pregnant women		59	25	43	
Maternal Age (years) *		29,51 ± 6,17	31,8 ±4,38	28,86 ±6,45	F = 2.2004, p = 0.139 [a]
Parity	**Multiparity** (No. women %)	21 35,6%	5 20,0%	10 23,3%	χ^2_{calc} = 2.932, df = 2, p = 0.231
	Primiparity (No.women,%)	38 64,4%	20 80,0%	33 76,7%	
Gestational age at onset (weeks) *		32,44 ±3,11	32,40 ±2,10	30,51 ±3,75	F = 5.155, p = 0.007[a]

Gestational age at birth (weeks) *		34,15 ±3,25	37,16 ±1,28	37,93 ±1,68	F = 31.827, p < 0.001 [a]
Weight of newborn (g) *		1864,86 ±549,05	3006,92 ±429,81	3114,67 ±382,03	F = 102.677, p <0.001 [a]
Origin	**Rural** (No.women,%)	37 (62,7%)	10 (40%)	24 (55,8%)	χ^2_{calc} = 3.675, df = 2, p = 0.159
	Urban (No.women,%)	22 (37,3%)	15 (60%)	19 (44,2%)	

a OneWay ANOVA Test; *median value+/- standard deviation, p < 0.05 significant different

TableXVIII. Paraclinical findings of studied subgroups

		PE	**GH**	**Control**	***P***
No. of pregnant women		59	25	43	
Renal	**Proteinuria/24h** (g/24 h) *	3,61 ±2,65	0,18 ±0,09	0,18 ±0,14	F = 56.252, p < 0.001 [a]
	Serum creatinine (mg/dL) *	0,81 ±0,20	0,54 ±0,03	0,53 ±0,04	F = 67.022, p < 0.001 [a]
Uric acid(mg/dL) *		4,99 ±0,74	3,31 ±0,32	3,16 ±0,36	F = 157.02, p < 0.001 [a]
Liver enzymes	**AST**(U/L) *	62,53 ±24,43	22,24 ±4,49	18,79 ±3,73	F = 99.272, p < 0.001 [a]
	ALT(U/L) *	53.92 ±16,88	13,16 ±3,34	11,26 ±2,84	F =201.532, p < 0.001 [a]
Platelet count (x10^4/uL) *		18,44 ±5,65	24,09 ±3,58	25,86 ±3,32	F = 35.413, p < 0.001 [a]
Serum albumin (mg/dL) *		2,06 ±0,54	3,78 ±0,41	4,26 ±0,43	F =284.758, p < 0.001 [a]

a OneWay ANOVA Test; *median value+/- standard deviation, p < 0.05 significant different

Utility of sFtl-1/PIGF ratio in diagnosis of preeclampsia

The mean value of sFtl-1/PIGF ratio of pregnant women with PE (No= 59) was 209.2 pg/mL with a standard deviation of 138.77 pg/mL, a median value of 251 pg/mL and an IQR (P_{75}-P_{25}) of 229 pg/mL; for the GH group (No = 25) was 46.08 pg/mL, with a standard deviation of 17.37 pg/mL, a median value of 43 pg/mL and a P_{75}-P_{25} of 29.5 pg/mL; and for the Control

group (No = 43) was 3.9 pg/mL with a standard deviation of 0.20 pg/mL, a median value of 3.90 mg / mL and a P_{75}-P_{25} of 0.30 pg/mL.

There were statistically significant differences between the **median values** of the sFtl-1/PIGF ratio of the three groups ($p < 0.001 < \alpha = 0.05$, Median test), respectively the **distribution of the sFtl-1/PIGF ratio values** were different in the analysed groups ($p < 0.001 < \alpha = 0.05$, Kruskal Wallis test for independent variables).

Table XIV. Specific values of sFtl-1/PIGF ratio for the studied groups

	PE	**GH**	**Control**	***p***
No. pregnant women	59	25	43	
sFtl-1/PIGF ratio (pg/mL) *	209±138,77	46,08±17,37	3,90±0,20	p < 0.001

*median value +/- standard deviation, p < 0.05 significant different

The area under the ROC curve (AUC) was estimated at 0.943 with confidence interval of 95% between (0.870 - 0.982). The statistical value of the test was z score= 18,843 and the p value $<0.0001 < \alpha = 0.05$, which is why the area under the curve was considered to be different from 0.5. The Youden index was 0.7844, and the value of the sFtl-1/PIGF ratio that distinguishes from the group with PE from GH was> 67 (pg/mL), with a sensitivity of 86.44% and a specificity of 92.00%.

Depending on the gestational age at onset of PE, the study groups were divided into 2 groups: early onset (<34 weeks) and late onset (> 34 weeks). There were statistically significant differences between the **median values** of the sFtl-1/ PIGF ratio between all groups for women with **early onset** ($p < 0.001 < \alpha = 0.05$, median test), respectively **distribution** of sFtl-1/PIGF ratio values for women with **early onset** were different in the analysed groups ($p < 0.001 < \alpha = 0.05$, Kruskal Wallis test for independent variables).

There were statistically significant differences between the **median values** of sFtl-1/PIGF ratio of the three groups for the pregnant women with **late-onset** ($p < 0.001 < \alpha = 0.05$, median test), at least two median values different, respectively the **distribution** of sFtl-1/PIGF ratio values for women with **late-onset** were different in the analysed groups ($p < 0.001 < \alpha = 0.05$, Kruskal Wallis test for independent variables). According to the Pairwise comparison test, there were significant differences between the pregnant women with late onset GH and PE with control group ($p < 0.001$), but there was no significant difference between the group of

pregnant women with late onset PE compared with the one with late onset GH (p = 0.102> 0.05).

Table XV. Values of sFtl-1/PIGF ratio(pg/mL) depending on gestational age at onset

	PE		**GH**		**Control**	
	Early Onset	Late Onset	Early Onset	Late Onset	Early Onset	Late Onset
No. pregnant women	35	24	17	8	32	11
Median	302.00	78.00	32.00	62.50	3.90	3.80
Minimum	64.00	39.00	19.00	36.00	3.50	3.60
Maximum	424.00	414.00	62.00	86.00	4.30	4.10

Depending on severity of PE, the study group included 23 (38.98%) pregnant women with mild PE and 36 (61.02%) pregnant women with severe PE. The median value of the sFtl-1/PIGF ratio in the group with mild PE (No = 23) was 77 pg/mL with a minimum of 39 pg/mL and a maximum of 98 pg/mL; for severe PE (N = 36) was 303 pg/mL, with a minimum of 49 pg/mL and a maximum of 424 pg/mL.

Table XVI. Values of sFtl-1/PIGF ratio (pg/mL) depending on severity of PE

	Severity of PE	
	Mild PE	**Severe PE**
No. pregnant women	23	36
Median	77.00	303.00
Minimum	39.00	49.00
Maximum	98.00	424.00

There were statistically significant differences between the **median values** of sFtl-1/PIGF ratio in the group with mild versus severe impairment (p <0.001 <α = 0.05, Median test), respectively the **distribution** of sFtl-1/PIGF ratio of women with mild impairment compared with severe impairment was different (p <0.001 <α = 0.05, MannWhitney U test for independent variables).

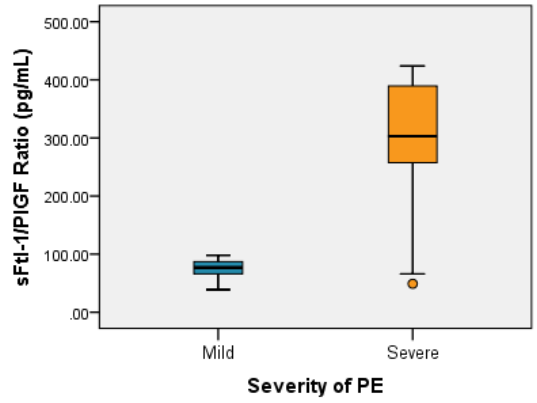

Figure 48. Box-whisker plots representing sFtl-1/PIGF ratio values depending on PE severity

The area under the ROC curve (AUC) was estimated at 0.940 with confidence interval of 95% between (0.845 - 0.985). The statistical value of the test was $z_{statistic}$ = 12,869 and the p value <0.0001 <α = 0.05, which is why the area under the curve was considered to be different from 0.5. The Youden index was 0.8454, and the value of the sFtl-1/PIGF ratio that distinguishes between the two groups Severe versus Mild PE was> 95 (pg/mL), with a sensitivity of 88.89% and a specificity of 95.65% (figure 49).

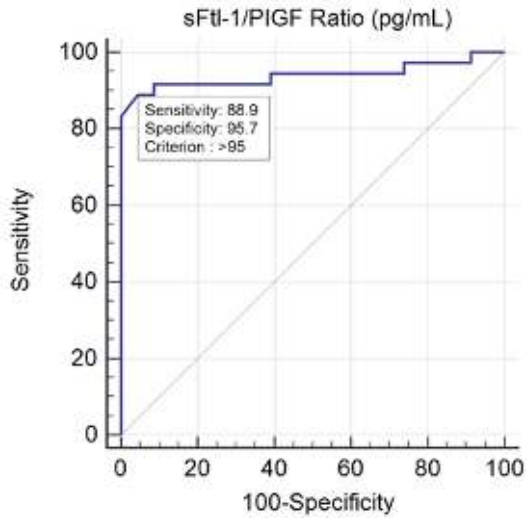

Figure 49. ROC curve of sFtl-1/PIGF ratio in mild versus severe PE

The risk of finding **severe PE** in pregnant women with **early onset** is 5,625 times higher than the risk of finding **severe PE** in pregnant women with **late onset** (OR = 5.625, 95% CI for OR = 1.794–17.633).

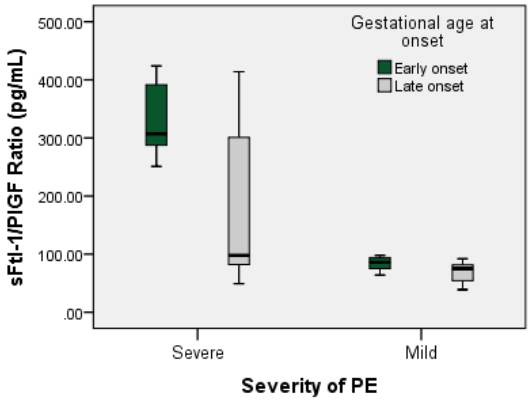

Figure 50. Box-whisker plots representing sFtl-1/PIGF ratio values depending on severity at onset of PE

Table XVIII. Values ofsFtl-1/PIGF ratio (pg/mL) in PE depending on severity and onset

	Severity of PE			
	Severe		**Mild**	
	Early Onset	**Late Onset**	**Early Onset**	**Late onset**
No	27	9	8	15
Med.	307.00	98.00	86.00	75.00
Min.	251.00	49.00	64.00	39.00
Max.	424.00	414.00	98.00	92.00

Pregnant women with **early onset PE** (<34 weeks) had the sFlt-1/PIGF ratio value higher in those with ***severe PE*** versus ***mild PE***, reaching the statistical significance (307 pg/mL compared to 86 pg/mL, $p = 0.011 < \alpha = 0.05$). Pregnant women with **late onset PE** (> 34 weeks) had a similar mean value of sFlt-1 / PIGF ratio in ***severe PE*** versus ***mild PE*** but reached statistical significance (98 pg/mL versus 75 pg/mL, $p = 0.033 < \alpha = 0.05$).

We also find significant differences between the median values of the sFtl-1/PIGF ratio in pregnant women with **severe PE** in the group of ***early onset*** compared to those with ***late onset*** (307 pg/mL, respectively 98 pg/mL, $p = 0.009 < \alpha = 0.05$) and the **distribution** of it reached the statistical significance. In contrast, the median value of sFtl-1/PIGF ratio in pregnant women with **mild PE** did not reach statistical significance in the group with ***early onset*** versus those with ***late onset*** (86 pg/mL, respectively 75 pg/mL, $p = 0.400 > \alpha = 0.05$).

Association of sFtl-1/PIGF ratio with remaining duration of pregnancy

Depending on the duration of pregnancy from the sFtl-1/PIGF test, the group of pregnant women with PE included 41 (69.49%) pregnant women who gave birth in less than 7 days and 18 pregnant women (30.51%) who gave birth in more than 7 days after testing. The **median value** of sFtl-1/PIGF ratio in the group of pregnant women with PE who gave birth ***in less*** than 7 days (No = 41) from testing was 289 pg/mL with a minimum of 48 pg/mL and a maximum of 424 pg/mL, respectively for the group of pregnant women with PE who gave birth ***in more*** than 7 days (No = 18) from testing was 85 pg/mL, with a minimum of 39 pg/mL and a maximum of 307 pg/mL.

Depending on the **median value** of sFtl-1/PIGF ratio, the subgroup with term ***less*** than 7 days was significantly higher than those with ***more*** than 7 days (206.88 pg/mL vs. 91.5

pg/mL, p <0.001 <α = 0.05). An association was found between remaining duration of pregnancy and the severity of PE, so **proportions** of ***severe PE*** with duration less than 7 days was significantly higher than the proportions of ***mild PE*** with duration less than 7 days.

Table XXII. The value of sFtl-1/PIGF ratio (pg/mL) depending on remaining duration of pregnancy and onset of PE

	Early onset		**Late onset**	
	Remaning duration of pregnancy		**Remaning duration of pregnancy**	
	<7 days	**> 7 days**	**<7 days**	**>7 days**
No pregnant women	26	9	15	9
Median	306.50	88.00	78.00	76.00
Minimum	251.00	64.00	48.00	39.00
Maximum	424.00	307.00	414.00	98.00

Analysing the group with **severe PE**, the values of sFlt-1/PIGF ratio for the pregnant women who gave birth in less than 7 days were significantly higher than those with more than 7 days (306 pg/mL vs 98 pg/mL, p = 0.012 <α = 0.05).Also, the statistic significance was reached for the group of pregnant women with ***early onset PE*** (306.5 pg/mL vs. 88 pg/mL, p = 0.042 <α = 0.05). There were no significant differences between the two subgroups in pregnant women with ***mild PE*** (76 pg/mL vs. 77 pg/mL, p = 0.998> α = 0.05) or ***late onset PE*** (78 pg/mL vs. 76 pg/mL, p = 0.996> α = 0.05).

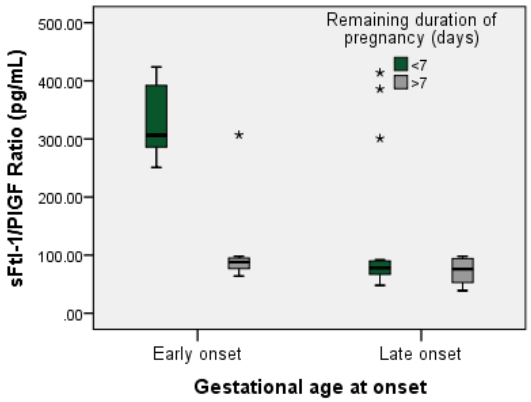

Figure 53. Box-whisker plots representing sFtl-1/PIGF ratio values in PE depending on the remaining duration of pregnancy and the onset of PE

The role of the serum albumin in the severity of PE

Albumin levels were significantly different between the group with ***severe PE*** and the group with ***mild PE*** (2.44 ± 0.36, respectively 1.82 ± 0.50). In order to set up the performance of serum albumin in clinical practice, there was constructed the ROC curve of the serum albumin, establishing a level of 2.3 g / dl which represents the threshold between the ***severe PE*** and the ***mild PE*** (sensitivity 88.89%, specificity 73.9%). We observed a strong association between albumin <2 g / dL and severe proteinuria (> 3 g / 24h) (χ^2_{calc}=8.310, df=1, p=0.004<α=0.05). The proportion of pregnant women with serum albumin <2 g / dL associated with proteinuria> 3 g / 24 h (64% of 25 pregnant women) was significantly different from the proportion of pregnant women with serum albumin <2 g / dL and proteinuria < 3 g / 24 h (26.5% of 34 pregnant women) (p <0.001).

Tabel XXIII. Albumin level depending on severity of PE

Severity of PE	Serum Albumin (g/dl)
Mild PE	2,44±0,36
Severe PE	1,82±0,50
t-test for independent samples	t = -5.507, df = 56.381, p < 0.001
Levene test for equality of variance	F = 8.72, p < 0.001

Association risk of severe PE group with serum albumin <2 g / dL was equal with the risk of association with serum albumin> 2 g / dL.

Tabele XXVI. Association risk of albumin levels with other paraclinical findings

	Association risk of Albumin level >2 g/dL *vs* <2 g/dL	
Decline of Renal function	equal	OR = 1.061, 95% CI pt. OR = 0.255–4.412
Abnormal Liver function	equal	OR = 0.556, 95% CI pt. OR = 0.140–2.200
Severe level of Proteinuria/24 h (nephrotic range)	equal	OR = 0.227, 95% CI pt. OR = 0.047–0.062

Maternal and foetal complications in the studied groups

According to data described in Table XXVII: there were significant differences between the values of gestational age at birth and the weight of the new-born birth for at least 2 of the analysed groups (p <0.001 <α = 0.05), establishing an association in studied groups with foetal complication as prematurity, respectively low birth weight (p <0.001 <α = 0.05).

Table XXVII. Maternal and fetal complications in the studied groups

	Studied group			*p*
	PE	**GH**	**Control**	
No. of pregnant women with foetal complications	46 (78%)	7 (28%)	6 (14%)	χ^2_{calc} = 45.236, df = 2, p <0.001
Gestational age at birth (weeks)*	34,5± 3,25	37,6± 1,28	37,93± 1,68	F = 31.827, p < 0.001 [a]
Prematurity	40 (67,8%)	6 (24,0%)	6 (14,0%)	χ^2_{calc} = 33.517, df = 2, p < 0.001
Weight of the new-born (g)*	1864,86 ±549,05	3006,92 ±429,81	3114,67 ±382,03	F = 102.677, p < 0.001 [a]
Low birth weight	46 (78%)	5 (20%)	5 (11,6%)	χ^2_{calc} = 51.733, df = 2, p < 0.001
No. of pregnant women with maternal complications	4 (6,8%)	0	0	-
Eclampsia	4(6,8%)	0	0	-
HELLP	1(1,7%)	0	0	-

([a] OneWay ANOVA; *median value+/- standard deviation, p < 0.05 significant different)

According to data from Table XXVIII, there are no significant differences of albumin levels depending on gestational age at birth, new-born weight (p> α = 0.05) and there is no association of the albumin levels with foetal complications, prematurity and low birth weight of the new-born (p> α = 0.05). The risk of foetal complications, prematurity and low birth weight in pregnant women with serum albumin> 2 (g / dL) is considered equal to the risk of foetal complications, prematurity and low birth weight in patients with serum albumin <2 (g / dL). The risks of foetal complications associated with levels of serum albumin divided into the 2 subgroups are shown in Table XXIX.

Table XXVIII. Maternal and fetal compliation in severe PE depending on albumin levels

		Serum albumin (g/dL)		*p*
		>2	**<2**	
No. of pregnant women with fetal complications		14 (87,5%)	19 (95,0%)	$\chi^2_{calc} = 0.655$, df = 1, p = 0.418
	Gestational age at birth (weeks)*	32,63±2,5	31,20±2,42	t = 1.843, df = 34, p = 0.074 [a] F = 0.011, p = 0.915 [b]
	Prematurity	13 (81,3%)	19 (95%)	$\chi^2_{calc} = 1.702$, df = 1, p = 0.192
	Weight at birth of newborn (g) *	1707,5 ±493,89	1482,6 ±437	t = 1.447, df = 34, p = 0.157 [a] F = 0.243, p = 0.625 [b]
	Low weight at birth (g)	14 (87,5%)	19 (95%)	$\chi^2_{calc} = 0.655$, df = 1, p = 0.418
No. of pregnant women with maternal complications		1 (6,3%)	3(15%)	?
	Eclampsia	1(6,3%)	3(15%)	?
	HELLP sdr	0	1 (5%)	?

([a] t-test for independent samples; [b] Levene test for equality of variance; *median value+/- standard deviation, $p < 0.05$ significant different)

Table XXIX. The risk of fetal complications associated with albumin levels

	Associated risk of Albumin level >2 g/dL vs. <2 g/dL	
Fetal complications	equal	OR = 0.368, 95% CI pt. OR = 0.030–4.478).
Prematurity	equal	OR = 0.228, 95% CI pt. OR = 0.021–2.441
Low birth weight	equal	OR = 0.368, 95% CI pt. OR = 0.030–4.478

Main conclusions: The sFtl-1/PIGF ratio may be an alternative method for diagnosing and classifying PE and can provide data about PE severity, in order to improve the therapeutical management of this special pathology. Levels of serum albumin below than 2 g/dL have not been shown to be an independent marker of severe PE, therefore the inclusion of plasma

albumin levels below 2 g/dL in the list of PE severity markers is at least questionable. The most common fetal complications of PE are prematurity and low birth weight.

General conclusions:

1. The sFtl-1/PIGF ratio can be a practical serological marker in the diagnostic certainty of PE and the differential diagnosis with GH and normotensive pregnant women, the positive limit value considered for for PE being over 65 pg/mL.

2. The highest value of sFtl-1/PIGF was found in the group of pregnant women with severe PE with early onset (307 pg/mL), followed by the group of pregnant women with late onset PE or GH which got similar values (78 pg/mL, respectively 62 pg/mL). The value of the control group (normotensive pregnant women) was 3.9 pg/mL.

3. The major contribution of the thesis for the clinical practice is that, for the first time in a national study, it was established a limit value of sFtl-1/PIGF ratio among pregnant women according to their pathological condition (PE, GH, Control group).

4. The sFtl-1/PIGF ratio can provide a prediction for PE and the remaining duration of pregnancy, and so, to guide the physician on the evolution and timing of pregnancy. A value of 95 pg/mL establishes the difference between severe PE and mild PE.

5. Serum albumin levels are not indicated to be included in the PE severity criteria.

6. Prematurity and low birth weight are the most common foetal complications associated with PE.

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Publications

Poster presentantions and articles from thesis published in extenso:

1.Elena Ciciu, Dragoș Făsie, Bogdan Cimpineanu, Liliana-Ana Tuță . Particular aspects of urinary tract infections during pregnancy. *5th International Multidisciplinary Scientific Conference on Social Sciences and Arts SGEM 2018*; 26 August - 01 September, 2018. 5 (3.3): 489-496.

ISSN: 2367-5659**. ISBN:** 978-619-7408-55-3.

DOI:10.5593/sgemsocial2018/3.3/S12.064

https://www.sgemsocial.org/index.php/elibrary?view=publication&task=show&id=743

2. Elena Ciciu, Ana-Maria Pașatu-Cornea, Liliana-Ana Tuță. Alport syndrome: a challenging cause of nephrotic syndrome during late pregnancy. *6th SWS International Scientifiv*

Conference on Social Sciences 2019; 26 August – 1 September, 2019; 6 (3): 383-392. **ISSN:**2682-9959. **ISBN:** 978-619-7408-93-5**.**

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https://sgemsocial.org/index.php/peer-review/jresearch?view=publication&task=show&id=4235

3. Elena Ciciu, Ana-Maria Pașatu-Cornea,Magda Nuțu, Andreea Grosu, Liliana-Ana Tuță. Pregnancy and CKD: always a challenge. *8th SWS Imternational Scientific Conference on Social Sciences ISCSS 2021;* 21-30 August, 2021; 8(1):791-*804.*

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https://www.sgemsocial.org/index.php/elibrary?view=publication&task=show&id=4694

Published abstract and oral presentations from thesis:

4.Elena Ciciu, Ana-Maria Pașatu-Cornea, Liliana-Ana Tuță. The impact of gestational age on anatomical and physiological changes of the upper urinary tract during pregnancy. *Nephrology Dialysis Transplantation,2021; 36(1)*„58th ERA-EDTA Congress", 5-8 June, 2021, Berlin

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https://academic.oup.com/ndt/article/36/Supplement_1/gfab107.006/6288562

Articles from thesis published in extenso :

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